Organic & Biomolecular Chemistry

Cite this: DOI: 10.1039/c2ob26390d

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PAPER

Metal-free catalyzed oxidative trimerization of indoles by using TEMPO in air: a biomimetic approach to 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-ones†

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Received 18th July 2012, Accepted 13th September 2012
DOI: 10.1039/c2ob26390d

A simple, convenient and efficient metal-free catalyzed oxidative trimeric reaction of indoles toward a variety of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives in moderate to excellent yields has been developed. This transformation proceeds *via* a tandem oxidative homocoupling reaction by using TEMPO in air as an environmentally benign oxidant. This methodology provides an alternative approach for the direct generation of all-carbon quaternary centers at the C3 position of indoles.

Introduction

The recent demand for highly efficient and environmentally benign syntheses of fine chemicals and pharmaceuticals has encouraged the development of mild, safe, and highly chemoselective oxidizers. The radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl radical) is now used extensively in organic synthesis and industrial applications as a mild, safe, and economical alternative to heavy metal reagents such as lead(IV), manganese(IV), chromium(VI), and mercury(II) as highly selective oxidation catalysts for the production of pharmaceuticals, flavors, fragrances, agrochemicals, and a variety of other specialty chemicals.[1]

Indole derivatives are important compounds that are widespread in nature and exhibit significant biological activity[2] and oxindole derivatives (Fig. 1) are known to possess a variety of biological activities.[3] For example, 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one **1** was isolated as the product of indole oxidation by a strain of *Claviceps purpurea*.[4a] This compound has also been characterised from natural (bacterial) sources such as *Vibrio parahaemolyticus*[3a] and *Haemophilus influenzae*.[4b] In addition, isatisine A **2**, an oxindole system having indole 2-substituents, is present in the roots and leaves of *Isatis indigotica* Fort. (Cruciferae). This biennial herbaceous plant is widely cultivated in China and East Asia for the prevention and treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis.[5] As such, developing convenient methods for the construction of 2,2-disubstituted indolin-3-ones is of considerable interest.[3d,5b,6] In 2008, Ganachaud and co-workers reported the biocatalytic synthesis of **1** by trimerisation of indole.[7a] However, the chemical synthesis of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one **1** and its derivatives from indoles still remained elusive,[7b,c] although there has been a report of its formation as a side product.[8] For example, Paola and co-workers reported that the oxidation of 5,6-dihydroxyindole in acidic aqueous media led to a mixture of 5,6-dihydroxy oxindole and trimer.[8] As part of ongoing work on transition metal-free oxidative homo coupling of indoles, we wish to report on successful metal-free catalyzed biomimetic oxidative trimerization of indoles toward 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one and its derivatives by using TEMPO in air as an oxidant.

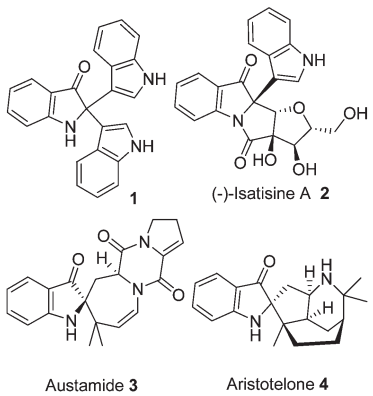

Fig. 1 Representative natural products with a 2,2′-disubstituent indolin-3-one structural unit.

Results and discussion

In early experiments, we found that the trimerization of indole took place in the presence of TEMPO (0.10 equiv.), pyridine (0.50 equiv.) and benzoic acid (0.50 equiv.) in CH_3CN at 50 °C, but the protocol led to the formation of a mixture of products **5a**

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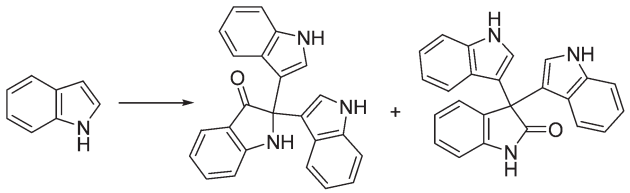
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob26390d



Condition A: TEMPO, pyridine, benzoic acid, CH_3CN, 50 °C, 2 days	**5a** 25%	**6** 9%
Condition B: TEMPO, benzoic acid, CH_3CN, 50 °C, 2 days	**5a** 28%	**6** 0%

Scheme 1 Trimeric reaction of indole by using TEMPO in air as an oxidant.

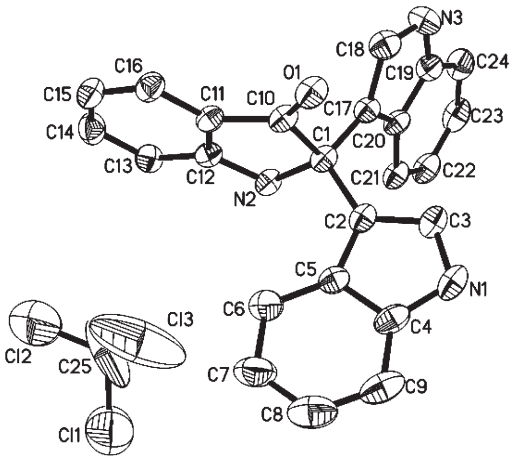


Fig. 2 ORTEP representation of the molecular structure of **5a** with H atoms omitted for clarity.

and **6** in low yields (Scheme 1, condition A). Changing pyridine to triethylamine, and carrying out the reaction either at room or elevated temperature was also not encouraging. Interestingly, a significant improvement in the regioselectivity was realized in the absence of pyridine, since **5a** was the sole trimerization product under the reaction conditions (Scheme 1, condition B), and its molecular structure was confirmed by X-ray crystallography (Fig. 2). The corresponding 3-(1*H*-indol-3-yl)-3,3′-biindolin-2-one product **6** was not identified.

Based on these promising initial results we decided to optimize the reaction conditions further to increase the reaction yield, and the results are summarized in Table 1. As shown in Table 1, the reaction showed a significant dependence on temperature. When the reaction was treated at 25 °C, trace amounts of **5a** were obtained (Table 1, entry 1). When the reaction mixture was warmed to 65 °C, the desired product was formed in 42% yield (Table 1, entry 5). A higher temperature (80 °C) led to a decreased yield possibly due to other side reactions (Table 1, entry 6).

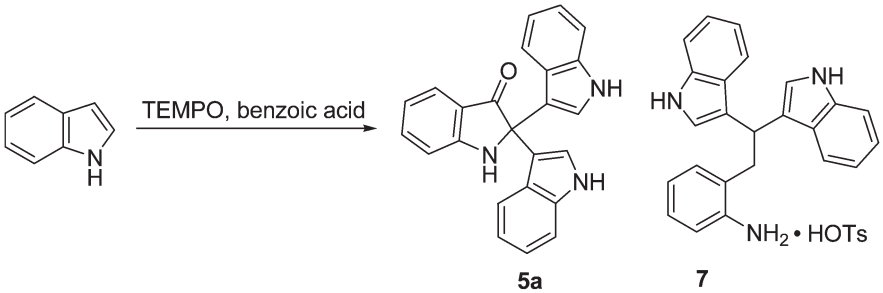
In addition, the corresponding reaction "on oxygene" gave a lower yield than air (Table 1, entry 7). It was also found that the use of TEMPO and benzoic acid is critical to the reaction. In the absence of TEMPO or benzoic acid, the trimerization reaction did not proceed (Table 1, entries 3 and 4). It was unexpected to find that the higher loading amounts of TEMPO result in a dramatic influence on the yield (Table 1, entries 8–15). For example, an 80% yield of trimerization production was obtained when using 0.70 equiv. of TEMPO (Table 1, entry 13). Interestingly, when more than 0.70 equiv. of TEMPO was employed, it led to a decreased yield (Table 1, entries 14 and 15). With respect to benzoic acid, it was also established that 0.50 equiv. of benzoic acid was indeed the preferred amount with lower or higher loading giving poor yields (Table 1, entries 13 and 22–25). Other acid additives, including substituted benzoic acid with various substituent groups and acetic acid, were also evaluated under the identical screening reaction conditions and gave lower yields than benzoic acid (Table 1, entries 16–20). Notably, when TsOH was used, an unexpected trimer **7** was obtained in excellent yield and selectivity (Table 1, entry 21).

The screening results demonstrated that the solvent effect has an important influence on the reaction, other solvents, such as $CHCl_3$, THF, xylene, and 1,4-dioxane, were effective for the reaction, but they were inferior to CH_3CN (Table 1, entries 26–29). Conversely, a trace amount of the desired product was detected when DMF, DMSO, or pyridine was employed as the solvent (Table 1, entries 31–33). After a great deal of screening on different parameters we found that the oxidative trimeric reaction of indole by using TEMPO (70 mol%) in air as an oxidant and benzoic acid (50 mol%) as an acid in acetonitrile at 65 °C led to the highest efficiency (80% yield, Table 1, entry 13).

After having optimized the conditions, the scope and generality of the reaction was studied. A variety of representative indole derivatives were subjected to the optimized conditions, as depicted in Table 2. Thus, a trimeric reaction of substituted indoles proceeded slowly to provide corresponding 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-one derivatives in moderate to excellent yields. The reaction can tolerate a variety of functional groups at the 1, 4, 5, 6, and 7 positions of indoles. The results have shown that electronegativities of substituents played a major role in governing the reactivity of the substrates. Electron-rich groups showed better results than electron-withdrawing groups in this trimerization. For example, *N*-(1*H*-indol-5-yl)acetamide was transformed into trimer **5g** in 93% yield (Table 2, entry 7). Substrates with a strong electron-withdrawing group at C-5, such as NO_2, disfavored the trimerization. When 5-nitro-1*H*-indole was subjected to the optimized conditions, no desired product was obtained (Table 2, entry 8), indicating a high level of sensitivity to the electronics of the indole ring, presumably because electron-withdrawing substituents reduce the reactivity of substrates in the acid-promoted dimerization of substrates.[8,9]

It is worth noting that some other substrates such as methyl 1*H*-indole-5-carboxylate and methyl 1*H*-indole-6-carboxylate gave a mixture of trimer and dimer under the present conditions due to their low reactivity. For instance, **5i** and **8b** were formed in 75% total yields with a ratio of 1 : 2 when methyl 1*H*-indole-5-carboxylate was subjected to the optimized conditions (Table 2, entry 10). Similarly, **5k** and **8c** were formed in 62% total yields with a ratio of 1 : 5 when methyl 1*H*-indole-6-carboxylate was subjected to the optimized conditions (Table 2, entry 12). In addition, only 15% of the dimer **8a** was obtained and no desired trimer was obtained when 1*H*-indole-5-

Table 1 Optimization of the reaction conditions[a]



5a **7**

Entry	TEMPO (mmol)	Acid (mmol)	Temp. (°C)	Solvent	Yield[b] (%)
1	0.1	Benzoic acid (0.5)	25	CH_3CN	Trace
2	0.1	Benzoic acid (0.5)	50	CH_3CN	30
3	0.1	0	50	CH_3CN	0
4	0	Benzoic acid (0.5)	50	CH_3CN	0
5	0.1	Benzoic acid (0.5)	65	CH_3CN	42
6	0.1	Benzoic acid (0.5)	80	CH_3CN	21
7	0.1	Benzoic acid (0.5)	65	CH_3CN	17[c]
8	0.2	Benzoic acid (0.5)	65	CH_3CN	45
9	0.3	Benzoic acid (0.5)	65	CH_3CN	48
10	0.4	Benzoic acid (0.5)	65	CH_3CN	52
11	0.5	Benzoic acid (0.5)	65	CH_3CN	57
12	0.6	Benzoic acid (0.5)	65	CH_3CN	69
13	0.7	Benzoic acid (0.5)	65	CH_3CN	80
14	0.8	Benzoic acid (0.5)	65	CH_3CN	69
15	1.0	Benzoic acid (0.5)	65	CH_3CN	60
16	0.7	*m*-Methoxybenzoic acid (0.5)	65	CH_3CN	70
17	0.7	*p*-Methylbenzoic acid (0.5)	65	CH_3CN	65
18	0.7	*p*-Nitrobenzoic acid (0.5)	65	CH_3CN	43
19	0.7	*o*-Nitrobenzoic acid (0.5)	65	CH_3CN	40
20	0.7	Acetic acid (0.5)	65	CH_3CN	Trace
21	0.7	TsOH (0.5)	65	CH_3CN	82[d]
22	0.7	Benzoic acid (0.15)	65	CH_3CN	30
23	0.7	Benzoic acid (0.3)	65	CH_3CN	40
24	0.7	Benzoic acid (0.7)	65	CH_3CN	46
25	0.7	Benzoic acid (1.0)	65	CH_3CN	48
26	0.7	Benzoic acid (0.5)	65	CH_3CN	77
27	0.7	Benzoic acid (0.5)	65	THF	65
28	0.7	Benzoic acid (0.5)	65	Xylene	61
29	0.7	Benzoic acid (0.5)	65	1,4-Dioxane	57
30	0.7	Benzoic acid (0.5)	65	HOAc	10
31	0.7	Benzoic acid (0.5)	65	DMF	Trace
32	0.7	Benzoic acid (0.5)	65	DMSO	Trace
33	0.7	Benzoic acid (0.5)	65	Pyridine	Trace

[a] Reaction conditions: indole (1.0 mmol), solvent (0.6 mL), and oil bath for 3 days. [b] Isolated yield. [c] Reaction conditions: indole (1.0 mmol), CH_3CN (0.6 mL) and O_2 (balloon, 1 atm) at 65 °C for 3 days. [d] Compound **7** was obtained.

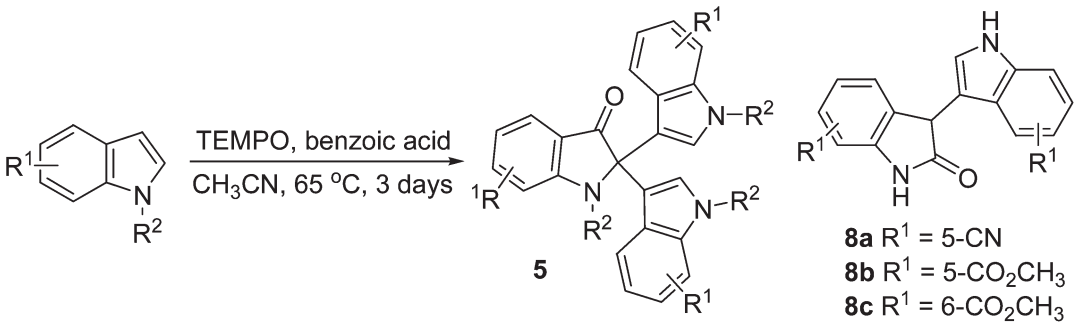
carbonitrile was subjected to the optimized conditions (Table 2, entry 9).

To confirm the effect of dioxygen, the trimeric reaction was attempted in the absence of dioxygen (Scheme 2). The result showed that the reaction was carried out inefficiently, and the desired product **5a** was obtained with a poor yield of 25%. The result demonstrated that dioxygen is necessary for an efficient trimeric reaction.

Conclusions

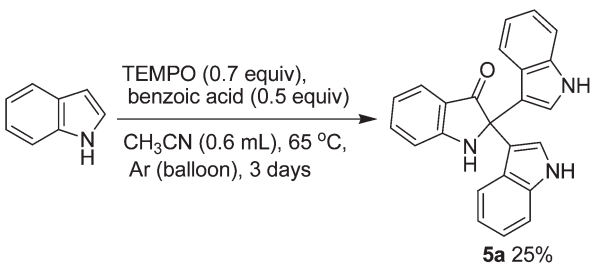
In summary, we have successfully developed a novel, operationally simple, and practical biomimetic synthetic method for the trimerization of indoles by using TEMPO in air as an oxidant with excellent regioselectivity under mild conditions. This reaction provides a novel method for the generation of all-carbon quaternary centers at the C3 position of indoles. Moreover, it has several advantages. (1) An inexpensive and environmentally friendly TEMPO has been used in air as an oxidant. (2) The operationally simple and metal-free procedure and broad substrate make it potentially useful. (3) It is highly regioselective (2,3′-linkage). (4) This trimeric reaction proceeds without exclusion of moisture or air from the reaction mixture and allows the isolation of the desired 2,2-disubstituted indolin-3-one derivatives in moderate to excellent yields. Currently, our method is limited to the homo trimerization of *N*-protected and free indole derivatives. The development of a cross-coupling trimerization is currently under way in our lab and will be the subject of future work.

Table 2 Trimeric reaction of indoles by using TEMPO in air as an oxidant[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	H	H	**5a**	80
2	5-Br	H	**5b**	68
3	5-F	H	**5c**	71
4	5-CH_3	H	**5d**	73
5	5-OCH_3	H	**5e**	76
6	5-OBn	H	**5f**	72
7	5-NHAc	H	**5g**	93
8	5-NO_2	H	**5h**	0
9	5-CN	H	**8a**	15
10	5-CO_2CH_3	H	**5i** + **8b**	75[c]
11	6-F	H	**5j**	54
12	6-CO_2CH_3	H	**5k** + **8c**	62[c]
13	7-CH_3	H	**5l**	92
14	4-OCH_3	H	**5m**	68
15	H	H	**5n**	70

[a] Reaction conditions: indole (1.0 mmol), benzoic acid (0.5 mmol), TEMPO (0.7 mmol), CH_3CN (0.6 mL), 65 °C. [b] Isolated yield. [c] Combined yield **5** and **8**.



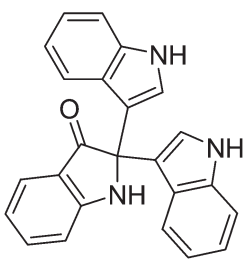
Scheme 2 Trimeric reaction of indole with TEMPO as an oxidant under an Ar atmosphere.

Experimental section

General

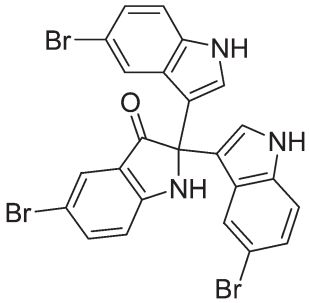
Melting points were determined on a digital melting point apparatus and temperatures were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra. $CDCl_3$ or DMSO-d_6 was used as the NMR solvent. Mass spectra were recorded with a Bruker Dalton Esquire 3000 plus LC-MS apparatus. Elemental analysis was carried out on a Perkin-Elmer 240B instrument. HRFABMS spectra were recorded on an FTMS apparatus. Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with an ethyl acetate–petroleum ether (PE) (60–90 °C) mixture.

General procedure for the preparation of 2-(1*H*-indol-3-yl)-2,3′-biindolin-3-ones. To a solution of indole (1.0 mmol) and TEMPO (0.7 mmol) in CH_3CN (0.6 mL) was added benzoic acid (0.5 mmol) under atmosphere and the mixture was stirred at 65 °C for 3 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc–PE = 1 : 2) to yield the corresponding product.

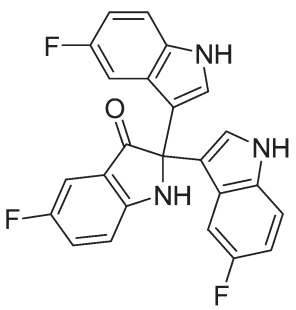


2-(1*H*-Indol-3-yl)-2,3′-biindolin-3-one, 5a. Yellow solid, mp: 241.5–244 °C (from EtOAc–PE = 1 : 2) (lit.[8] mp: 243–245.5). IR (KBr) ν_{max}: 3375, 3296, 1677, 1612, 1462, 1328, 1098, 746 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.94 (s, 1H, NH, D_2O exchangeable), 10.93 (s, 1H, NH, D_2O exchangeable), 8.10 (s, 1H, NH, D_2O exchangeable), 7.45 (t, J = 8.0 Hz, 1H, Ar-H), 7.43 (d, J = 7.6 Hz, 1H, Ar-H), 7.32 (d, J = 8.0 Hz, 2H, Ar-H),

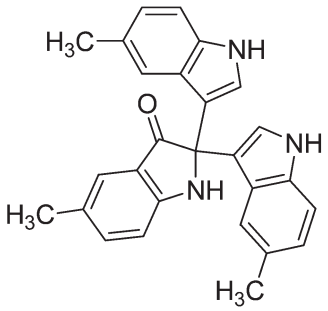
7.28 (d, J = 8.0 Hz, 2H, Ar-H), 7.05 (d, J = 2.5 Hz, 2H, Ar-H), 6.99 (dt, J = 1.0, 8.0 Hz, 2H, Ar-H), 6.91 (d, J = 8.0 Hz, 1H, Ar-H), 6.78 (dt, J = 1.0, 8.0 Hz, 2H, Ar-H), 6.69 (dt, J = 1.0, 7.6 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.3, 161.0, 137.9, 137.4, 126.1, 124.9, 124.5, 121.5, 121.0, 118.8, 118.2, 117.5, 114.4, 112.3, 112.1, 68.1. HRESIMS calcd for $[C_{24}H_{17}ON_3 + H]^+$ 364.1450, found 364.1443. These assignments matched those previously published.[4]



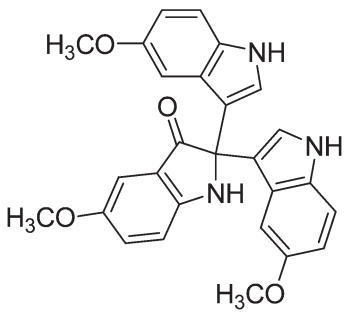
5,5′-Dibromo-2-(5-bromo-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5b. Yellow solid, mp: 247–249 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3448, 3395, 3318, 1682, 1623, 1494, 1427, 1103, 795 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H, NH), 11.26 (s, 1H, NH), 8.51 (s, 1H, NH), 7.62 (dd, J = 8.6, 2.4 Hz, 1H, Ar-H), 7.58 (d, J = 2.0 Hz, 1H, Ar-H), 7.36 (d, J = 2.0 Hz, 2H, Ar-H), 7.32 (d, J = 8.6 Hz, 2H, Ar-H), 7.19 (d, J = 2.4 Hz, 2H, Ar-H), 7.13 (dd, J = 8.6, 2.0 Hz, 2H, Ar-H), 6.92 (d, J = 8.6 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.5, 159.6, 140.5, 136.2, 127.6, 127.1, 125.9, 124.3, 122.8, 119.4, 114.6, 114.4, 113.3, 111.8, 108.8, 68.2. HRESIMS calcd for $[C_{24}H_{14}ON_3Br_3 + H]^+$ 597.8765, 599.8745, 601.8724, found 597.8759, 599.8732, 601.8708.



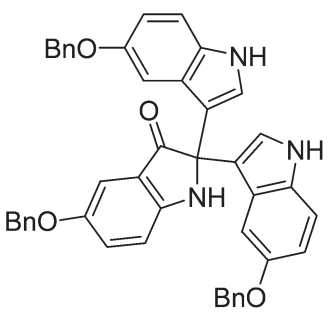
5,5′-Difluoro-2-(5-fluoro-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5c. Yellow solid, mp: 90–92 °C (from EtOAc–PE = 1 : 4). IR (KBr) ν_{max}: 3406 (br s), 1692, 1489, 1455, 1255, 1177, 802 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 2H, NH), 7.33 (dd, J = 8.8, 2.6 Hz, 1H, Ar-H), 7.26 (dt, J = 2.6, 8.8 Hz, 1H, Ar-H), 7.19 (d, J = 8.8 Hz, 1H, Ar-H), 7.18 (d, J = 8.8 Hz, 1H, Ar-H), 7.07 (d, J = 2.6 Hz, 2H, Ar-H), 7.01 (d, J = 2.4 Hz, 1H, Ar-H), 6.98 (d, J = 2.4 Hz, 1H, Ar-H), 6.87 (dd, J = 9.0, 3.0 Hz, 2H, Ar-H), 6.84 (dd, J = 9.0, 3.0 Hz, 1H, Ar-H), 5.3 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.0, 158.8, 157.0, 156.5, 133.5, 126.0 (d, J = 26.0 Hz), 125.7 (d, J = 9.9 Hz), 125.5, 120.2 (d, J = 7.3 Hz), 114.5 (d, J = 4.7 Hz), 114.3 (d, J = 7.3 Hz), 112.2 (d, J = 9.9 Hz), 110.9 (d, J = 26.0 Hz), 110.1 (d, J = 23.4 Hz), 105.2 (d, J = 23.4 Hz), 69.0. HRESIMS calcd for $[C_{24}H_{14}ON_3F_3 + H]^+$ 418.1167, found 418.1162.



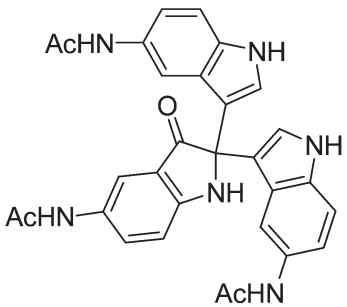
5,5′-Dimethyl-2-(5-methyl-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5d. Yellow solid, mp: 161–163 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3449, 3385, 3322, 1683, 1623, 1494, 1427, 796 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H, NH), 10.76 (s, 1H, NH), 7.79 (s, 1H, NH), 7.31 (dd, J = 8.4, 1.7 Hz, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 7.20 (d, J = 8.1 Hz, 2H, Ar-H), 7.07 (s, 2H, Ar-H), 6.98 (d, J = 2.5 Hz, 2H, Ar-H), 6.85 (d, J = 8.4 Hz, 1H, Ar-H), 6.82 (dd, J = 8.4, 1.3 Hz, 2H, Ar-H), 2.21 (s, 3H, CH_3), 2.18 (s, 6H, 2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.3, 159.6, 139.1, 135.8, 126.9, 126.4, 126.3, 124.5, 124.1, 123.1, 120.7, 118.5, 114.1, 112.4, 111.7, 68.5, 21.9, 20.6. HRESIMS calcd for $[C_{27}H_{23}ON_3 + H]^+$ 406.1919, found 406.1905.



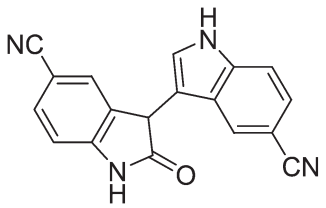
5,5′-Dimethoxy-2-(5-methoxy-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5e. Yellow solid, mp: 226–228 °C (from EtOAc–PE = 1 : 3) (lit.[1] mp: 201–203). IR (KBr) ν_{max}: 3404, 3033, 1679, 1489, 1445, 1214, 1022 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.77 (s, 1H, NH), 10.76 (s, 1H, NH), 7.77 (s, 1H, NH), 7.23 (s, J = 8.8 Hz, 2H, Ar-H), 7.19 (d, J = 2.7 Hz, 1H, Ar-H), 7.02 (d, J = 2.6 Hz, 2H, Ar-H), 6.95 (d, J = 2.6 Hz, 1H, Ar-H), 6.92 (d, J = 8.8 Hz, 1H, Ar-H), 6.79 (d, J = 2.4 Hz, 2H, Ar-H), 6.69 (d, J = 2.4 Hz, 1H, Ar-H), 6.66 (d, J = 2.4 Hz, 1H, Ar-H), 3.69 (s, 3H, CH_3), 3.51 (s, 6H, 2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.7, 157.3, 153.0, 152.2, 132.6, 128.2, 126.5, 125.2, 118.5, 114.1, 113.9, 112.5, 111.0, 105.0, 103.5, 68.9, 56.0, 55.5. HRESIMS calcd for $[C_{27}H_{23}O_4N_3 + H]^+$ 454.1767, found 454.1749.



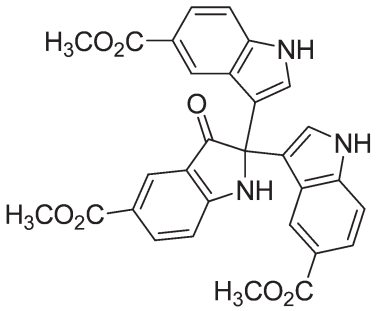
5,5′-Bis(benzyloxy)-2-(5-benzyloxy-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5f. Yellow solid, mp: 91–92 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3399 (br s), 1688, 1488, 1455, 1203 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 2H, NH), 7.40–7.35 (m, 3H, Ar-H), 7.33 (s, 1H, NH), 7.32–7.24 (m, 13H, Ar-H), 7.22 (d, J = 2.4 Hz, 1H, Ar-H), 7.13 (d, J = 8.8 Hz, 2H, Ar-H), 6.92 (d, J = 2.3 Hz, 2H, Ar-H), 6.90 (d, J = 2.3 Hz, 2H, Ar-H), 6.86 (d, J = 2.4 Hz, 1H, Ar-H), 6.84 (d, J = 2.4 Hz, 1H, Ar-H), 6.80 (d, J = 8.8 Hz, 1H, Ar-H), 4.96 (s, 2H, CH_2), 4.82 (s, 4H, $2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 156.4, 153.0, 152.9, 137.5, 136.7, 132.3, 128.8, 128.6, 128.5, 128.1, 127.7, 127.6, 127.5, 126.0, 125.0, 120.5, 114.7, 114.4, 113.0, 112.3, 106.4, 103.8, 70.7, 70.6, 69.3. HRESIMS calcd for $[C_{45}H_{35}O_4N_3 + H]^+$ 682.2706, found 682.2692.



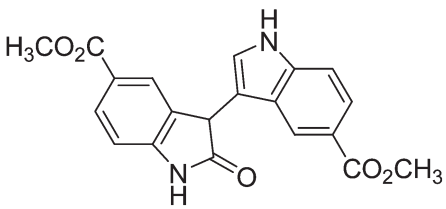
***N*,*N*′-(2-(5-Acetamido-1*H*-indol-3-yl)-3-oxo-2,3′-biindoline-5,5′-diyl)diacetamide, 5g.** Yellow solid, mp: 153–155 °C (from EtOAc–EtOH = 10 : 1). IR (KBr) ν_{max}: 3271 (br s), 1662, 1621, 1553, 1492, 1375 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.90 (s, 2H, NH), 9.88 (s, 1H, NH), 9.61 (s, 2H, NH), 7.75 (d, J = 1.8 Hz, 1H, Ar-H), 7.64 (s, 1H, NH), 7.56 (dd, J = 8.8, 2.0 Hz, 1H, Ar-H), 7.39 (dd, J = 8.8, 1.8 Hz, 2H, Ar-H), 7.29 (s, 2H, Ar-H), 7.22 (d, J = 8.8 Hz, 2H, Ar-H), 7.01 (d, J = 2.4 Hz, 2H, Ar-H), 6.89 (d, J = 8.8 Hz, 1H, Ar-H), 1.99 (s, 3H, CH_3), 1.89 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 201.1, 168.2, 168.0, 157.8, 134.3, 131.3, 130.5, 129.7, 128.8, 125.9, 125.3, 117.8, 116.2, 114.3, 112.7, 112.1, 111.5, 68.9, 24.2, 24.1. HRESIMS calcd for $[C_{30}H_{26}O_4N_6 + H]^+$ 535.2094, found 535.2084.



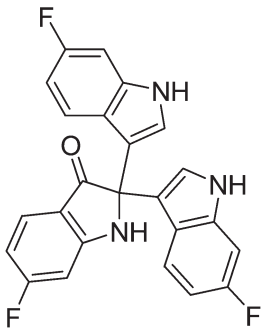
2-Oxo-3,3′-biindoline-5,5′-dicarbonitrile, 8a. White solid, mp: 67–68 °C (from EtOAc–PE = 1 : 1). IR (KBr) ν_{max}: 3322 (br s), 2225, 1728, 1619, 1484, 1122 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.67 (s, 1H, NH), 10.90 (s, 1H, NH), 8.22 (s, 1H, Ar-H), 7.79 (dd, J = 8.1, 1.6 Hz, 1H, Ar-H), 7.75 (d, J = 2.5 Hz, 1H, Ar-H), 7.53 (d, J = 8.5 Hz, 1H, Ar-H), 7.45 (dd, J = 8.5, 1.6 Hz, 1H, Ar-H), 7.09 (d, J = 2.5 Hz, 1H, Ar-H), 7.06 (d, J = 8.1 Hz, 1H, Ar-H), 6.78 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.4, 146.5, 139.2, 135.3, 133.9, 128.8, 127.5, 126.9, 125.4, 124.5, 121.2, 119.8, 115.6, 113.6, 111.2, 104.5, 101.3, 74.6. MS (ESI): 299 (M + H^+, 100), 321 (M + Na^+, 10). Anal calcd for $C_{18}H_{10}N_4O$: C, 72.23; H, 3.70; N, 18.72. Found C, 72.05; H, 4.07; N, 18.45.



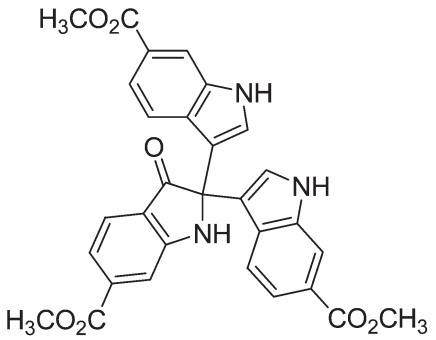
Dimethyl 2-(5-(methoxycarbonyl)-1*H*-indol-3-yl)-3-oxo-2,3′-biindoline-5,5′-dicarboxylate, 5i. Yellow solid, mp: 111–113 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3337 (br s), 1702, 1618, 1436, 1310, 1249 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.48 (s, 1H, NH), 11.47 (s, 1H, NH), 9.16 (s, 1H, NH), 8.08 (dd, J = 8.7, 1.6 Hz, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 8.00 (s, 2H, Ar-H), 7.67 (dd, J = 8.6, 1.6 Hz, 2H, Ar-H), 7.43 (d, J = 8.6 Hz, 2H, Ar-H), 7.27 (d, J = 2.4 Hz, 2H, Ar-H), 6.99 (d, J = 8.7 Hz, 1H, Ar-H), 3.78 (s, 3H, CH_3), 3.69 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.9, 167.5, 166.2, 162.8, 140.1, 129.0, 127.4, 126.5, 125.3, 123.6, 122.8, 120.7, 118.7, 117.4, 114.9, 112.3, 112.0, 68.6, 52.3, 52.1. HRESIMS calcd for $[C_{30}H_{23}O_7N_3 + H]^+$ 538.1614, found 538.1597.



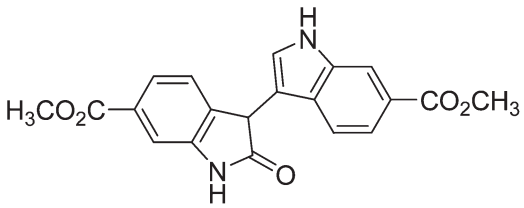
Dimethyl 2-oxo-3,3′-biindoline-5,5′-dicarboxylate, 8b. White solid, mp: 144–146 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3332 (br s), 1705, 1620, 1435, 1315, 1256 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.40 (d, J = 2.3 Hz, 1H, NH), 10.79 (s, 1H, NH), 8.36 (s, 1H, Ar-H), 7.92 (dd, J = 8.2, 1.8 Hz, 1H, Ar-H), 7.81 (d, J = 1.8 Hz, 1H, Ar-H), 7.67 (dd, J = 8.6, 1.8 Hz, 1H, Ar-H), 7.40 (d, J = 8.6 Hz, 1H, Ar-H), 7.03 (d, J = 2.3 Hz, 1H, Ar-H), 7.00 (d, J = 8.2 Hz, 1H, Ar-H), 6.64 (s, 1H), 3.78 (s, 3H, CH_3), 3.75 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.8, 167.7, 166.5, 146.8, 140.0, 133.7, 132.1, 126.0, 125.8, 125.1, 124.3, 123.6, 122.7, 120.6, 116.7, 112.1, 110.2, 74.9, 52.3, 52.1. MS (ESI): 365 (M + H^+, 100), 387 (M + Na^+, 25). Anal calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found C, 66.12; H, 4.29; N, 7.92.



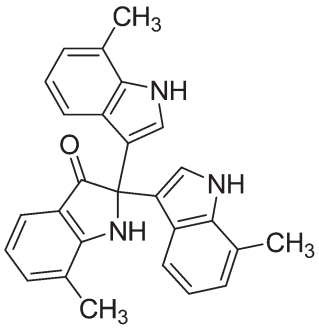
6,6′-Difluoro-2-(6-fluoro-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5j. Yellow solid, mp: 78–79 °C (from EtOAc–PE = 1 : 1). IR (KBr) ν_{max}: 3469, 3355 (br s), 1675, 1625, 1592, 1457, 1300, 1144, 1096 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 2H, NH), 8.54 (s, 1H, NH), 7.55 (dd, J = 8.6, 5.8 Hz, 1H, Ar-H), 7.24 (dd, J = 8.6, 5.8 Hz, 2H, Ar-H), 7.16 (dd, J = 10.2, 2.4 Hz, 2H, Ar-H), 7.12 (d, J = 2.4 Hz, 2H, Ar-H), 6.75 (dt, J = 2.4, 9.4 Hz, 2H, Ar-H), 6.64 (dd, J = 10.2, 2.1 Hz, 1H, Ar-H), 6.54 (dt, J = 2.1, 9.4 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 199.1, 162.3 (d, J = 14.6 Hz), 158.0, 137.2 (d, J = 12.8 Hz), 129.7, 129.0, 127.9 (d, J = 12.8 Hz), 125.1, 122.7, 121.7 (d, J = 10.1 Hz), 114.9, 114.2, 107.6 (d, J = 14.6 Hz), 106.1 (d, J = 25.0 Hz), 98.0 (d, J = 25.0 Hz), 68.5. HRESIMS calcd for $[C_{24}H_{14}ON_3F_3 + H]^+$ 418.1167, found 418.1162.



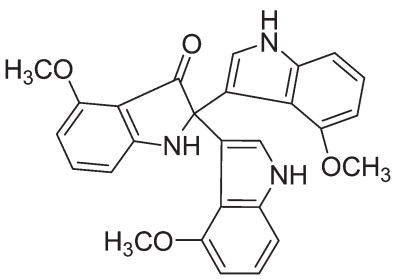
Dimethyl 2-(6-(methoxycarbonyl)-1*H*-indol-3-yl)-3-oxo-2,3′-biindoline-6,6′-dicarboxylate, 5k. Yellow solid, mp: 154–156 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3349 (br s), 1708, 1621, 1454, 1319, 1277, 1218 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.48 (s, 1H, NH), 11.47 (s, 1H, NH), 8.50 (s, 1H, NH), 7.58 (d, J = 8.0 Hz, 1H, Ar-H), 8.02 (s, 2H, Ar-H), 7.50 (s, 1H, Ar-H), 7.44 (dd, J = 8.5, 1.2 Hz, 2H, Ar-H), 7.38 (d, J = 2.5 Hz, 2H, Ar-H), 7.27 (d, J = 8.5 Hz, 2H, Ar-H), 7.25 (dd, J = 8.0, 1.2 Hz, 1H, Ar-H), 3.84 (s, 3H, CH_3), 3.78 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 200.8, 167.5, 166.4, 160.5, 138.0, 136.8, 129.4, 129.0, 128.5, 125.6, 122.8, 120.9, 120.5, 119.7, 118.1, 114.3, 113.2, 68.4, 53.0, 52.3. HRESIMS calcd for $[C_{30}H_{23}O_7N_3 + H]^+$ 538.1614, found 538.1600.



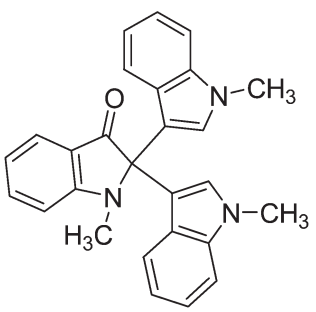
Dimethyl 2-oxo-3,3′-biindoline-6,6′-dicarboxylate, 8c. White solid, mp: 240–242 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3329 (br s), 1703, 1617, 1436, 1312, 1253 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.43 (d, J = 2.3 Hz, 1H, NH), 10.57 (s, 1H, NH), 8.00 (s, 1H, Ar-H), 7.60 (dd, J = 7.7, 1.2 Hz, 1H, Ar-H), 7.56 (dd, J = 8.5, 1.0 Hz, 1H, Ar-H), 7.51 (dd, J = 8.5, 1.2 Hz, 1H, Ar-H), 7.41 (d, J = 1.0 Hz, 1H, Ar-H), 7.38 (d, J = 7.7 Hz, 1H, Ar-H), 7.25 (d, J = 2.3 Hz, 1H, Ar-H), 6.64 (s, 1H), 3.82 (s, 3H, CH_3), 3.79 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.4, 167.6, 166.4, 142.5, 138.6, 136.6, 130.9, 128.9, 127.9, 125.4, 123.9, 122.8, 120.8, 119.7, 115.7, 114.1, 110.3, 75.0, 52.7, 52.2. MS (ESI): 365 (M + H^+, 100), 387 (M + Na^+, 25). Anal calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found C, 65.79; H, 4.71; N, 7.60.



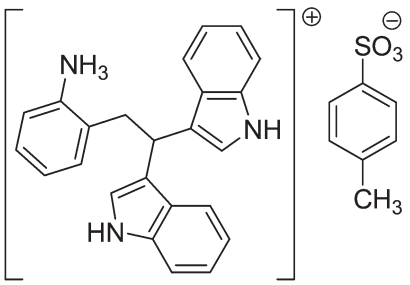
7,7′-Dimethyl-2-(7-methyl-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5l. Yellow solid, mp: 121–123 °C (from EtOAc–PE = 1 : 2). IR (KBr) ν_{max}: 3410 (br s), 1692, 1606, 1498, 1433, 786, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H, NH), 8.07 (s, 1H, NH), 7.59 (d, J = 7.5 Hz, 1H, Ar-H), 7.33 (d, J = 7.0 Hz, 1H, Ar-H), 7.23 (d, J = 8.8 Hz, 2H, Ar-H), 6.96–6.87 (m, 6H, Ar-H), 6.83 (t, J = 7.5 Hz, 1H, Ar-H), 5.28 (s, 1H), 2.39 (s, 6H, $2CH_3$), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 159.7, 137.5, 136.6, 125.3, 124.3, 122.8, 122.6, 122.0, 120.8, 120.0, 119.6, 119.5, 118.0, 115.3, 68.5, 16.6, 15.8. HRESIMS calcd for $[C_{27}H_{23}ON_3 + H]^+$ 406.1919, found 406.1905.



4,4′-Dimethoxy-2-(4-methoxy-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5m. Red solid, mp: 185–187 °C (from EtOAc–PE = 2 : 1). IR (KBr) ν_{max}: 3389 (br s), 1687, 1613, 1501, 1262, 1088 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 2H, NH), 7.25 (t, J = 8.1 Hz, 1H, Ar-H), 7.04 (s, 1H, N-H), 6.94 (t, J = 7.8 Hz, 2H, Ar-H), 6.76 (d, J = 8.1 Hz, 2H, Ar-H), 6.53 (s, 2H, Ar-H), 6.38 (d, J = 7.8 Hz, 2H, Ar-H), 6.31 (d, J = 8.1 Hz, 1H, Ar-H), 6.12 (d, J = 8.1 Hz, 1H, Ar-H), 3.88 (s, 3H, CH_3), 3.46 (s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 161.1, 159.3, 153.0, 138.7, 137.5, 125.2, 122.4, 116.4, 114.5, 109.9, 105.1, 104.8, 100.2, 98.2, 67.5, 55.6, 54.9. HRESIMS calcd for $[C_{27}H_{23}O_4N_3 + H]^+$ 454.1767, found 454.1754.



1,1′-Dimethyl-2-(1-methyl-1*H*-indol-3-yl)-2,3′-biindolin-3-one, 5n. Yellow solid, mp: 271–273 °C (from EtOAc–PE = 1 : 4). IR (KBr) ν_{max}: 3050, 1697, 1614, 1325, 1293 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (dt, J = 7.3, 1.0 Hz, 2H, Ar-H), 7.35 (d, J = 8.1 Hz, 2H, Ar-H), 7.29 (d, J = 8.1 Hz, 2H, Ar-H), 7.17 (dt, J = 8.1, 1.0 Hz, 2H, Ar-H), 6.99 (s, 2H, Ar-H), 6.96 (dt, J = 8.1, 1.0 Hz, 2H, Ar-H), 6.82 (d, J = 8.1 Hz, 1H, Ar-H), 6.73 (t, J = 7.3 Hz, 1H, Ar-H), 3.71 (s, 6H, $2CH_3$), 2.95 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 159.8, 137.8, 137.7, 129.3, 126.3, 125.7, 121.7, 121.6, 119.4, 118.6, 116.8, 111.3, 109.4, 107.9, 72.8, 32.9, 29.5. HRESIMS calcd for $[C_{27}H_{23}ON_3 + Na]^+$ 428.1739, found 428.1709.



2-(2,2-Di(1*H*-indol-3-yl)ethyl)benzenaminium benzenesulfonate, 7. Waxy solid. IR (KBr) ν_{max}: 3250 (br s), 1603, 1496, 1450, 1078 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.72 (s, 1H, NH), 10.71 (s, 1H, NH), 9.90–9.30 (s, 3H, NH), 7.51 (d, J = 8.0 Hz, 2H, Ar-H), 7.46 (d, J = 8.0 Hz, 2H, Ar-H), 7.27 (d, J = 8.0 Hz, 1H, Ar-H), 7.25 (d, J = 8.0 Hz, 2H, Ar-H), 7.21 (d, J = 2.2 Hz, 2H, Ar-H), 7.15 (dt, J = 2.2, 8.0 Hz, 1H, Ar-H), 7.07 (d, J = 8.0 Hz, 2H, Ar-H), 7.03 (s, 2H, Ar-H), 6.96 (t, J = 7.3 Hz, 2H, Ar-H), 6.83 (t, J = 7.3 Hz, 2H, Ar-H), 4.94 (t, J = 7.8 Hz, 1H), 3.58 (d, J = 7.8 Hz, 2H), 2.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.9, 138.3, 136.9, 134.4, 131.6, 130.5, 128.6, 127.6, 127.3, 127.0, 126.0, 123.2, 122.8, 121.1, 119.5, 118.4, 118.3, 111.8, 35.5, 32.3, 21.2. MS (ESI): 524 ($M + H^+$, 100).

Acknowledgements

The authors are grateful to the NSF of China (Nos: 21162001 and 21202023), the National Key Technology R&D Program of China (No: 2009BAI78B01), Jiangxi Province Key Support Program (No: 2009BNB06200), Natural Science Foundation of Jiangxi Province (No: 2009GZH0013) and Jiangxi Province Office of Education Support Program (No: GJJ10718) for financial support.

Notes and references

1 For reviews on the application of TEMPO and its derivatives in organic synthesis, see: (*a*) R. A. Sheldon, I. W. C. E. Arends, G. J. T. Brink and A. Dijksman, *Acc. Chem. Res.*, 2002, **35**, 774–781; (*b*) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal.*, 2004, **346**, 1051–1071; (*c*) L. Tebben and A. Studer, *Angew. Chem., Int. Ed.*, 2011, **50**, 5034–5068; (*d*) R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2010, **14**, 245–251; (*e*) J. Piera and J.-E. Bäckvall, *Angew. Chem., Int. Ed.*, 2008, **47**, 3506–3523; (*f*) B.-Z. Zhan and A. Thompson, *Tetrahedron*, 2004, **60**, 2917–2935.

2 (*a*) R. J. Sundberg, *Indoles*, Academic Press, San Diego, 1996; (*b*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920; (*c*) L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673–714; (*d*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608–9644; (*e*) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449–4465.

3 (*a*) A. Gazit, N. Osherov, I. Posner, P. Yaish, E. Poradosu, C. Gilon and A. Levitzki, *J. Med. Chem.*, 1991, **34**, 1896–1907; (*b*) S. Dilber, M. Saban, J. Jelaca, A. Gelineo, L. Arsenijevic and M. Bogavac, *Pharmazie*, 1989, **44**, 649–650; (*c*) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354–7358; (*d*) C. V. S. Kumar, V. G. Puranik and C. V. Ramana, *Chem.–Eur. J.*, 2012, **18**, 9601–9611.

4 (*a*) R. Bell, S. Carmeli and N. Sar, *J. Nat. Prod.*, 1994, **57**, 1587–1590; (*b*) T. L. Stull, L. Hyun, C. Sharetzsky, J. Wooten, J. P. McCauley and A. B. Smith III, *J. Biol. Chem.*, 1995, **270**, 5–8.

5 (*a*) J.-F. Liu, Z.-Y. Jiang, R.-R. Wang, Y.-T. Zheng, J.-J. Chen, X.-M. Zhang and Y.-B. Ma, *Org. Lett.*, 2007, **9**, 4127–4129; (*b*) J. Lee and J. S. Panek, *Org. Lett.*, 2011, **13**, 502–505; (*c*) H.-Z. Zheng, Z.-H. Dong and Q. Yu, *Modern Study of Traditional Chinese Medicine*, Xueyaun Press, Beijing, China, 1997, vol. 1, pp. 328–334.

6 (*a*) X. Zhang, T. Mu, F.-X. Zhan, L.-J. Ma and G.-X. Liang, *Angew. Chem., Int. Ed.*, 2011, **50**, 6164–6166; (*b*) A. Wetzel and F. Gagosz, *Angew. Chem., Int. Ed.*, 2011, **50**, 7354–7358; (*c*) M. Rueping, S. Raja and A. Núñez, *Adv. Synth. Catal.*, 2011, **353**, 563–568; (*d*) W. Wu, M.-X. Xiao, J.-B. Wang, Y. Li and Z.-X. Xie, *Org. Lett.*, 2012, **14**, 1624–1627; (*e*) A. Karadeolian and M. A. Kerr, *J. Org. Chem.*, 2010, **75**, 6830–6841; (*f*) A. Karadeolian and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2011, **49**, 1133–1135.

7 (*a*) C. Ganachaud, V. Garfagnoli, T. Tron and G. Iacazio, *Tetrahedron Lett.*, 2008, **49**, 2476–2478; (*b*) K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi and A. Khorshidi, *Can. J. Chem.*, 2009, **87**, 1213–1217; (*c*) K. Rad-Moghadam, M. Shari-Kiasaraie and H. Taheri-Amlashi, *Tetrahedron*, 2010, **66**, 2316–2321.

8 P. Manini, M. d'Ischia, M. Milosa and G. Prota, *J. Org. Chem.*, 1998, **63**, 7002–7008.

9 (*a*) N. Wahlström, J. Slätt, B. Stensland, A. Ertan, J. Bergman and T. Janosik, *J. Org. Chem.*, 2007, **72**, 5886–5889; (*b*) H. Ishii, K. Murakami, E. Sakurada, K. Hosoya and Y. Murakam, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2377–2385.